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PERSPECTIVES

Re-thinking the ethics of dual-use research of concern on transmissible pathogens

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Abstract Rapid acceleration in the science of genetic engineering of infectious diseases has outpaced legal and ethical frameworks for dealing with such research. Dual-use research of concern (DURC), which can be used for good or for harm, raises new questions about potential harm to human beings which have not traditionally been considered by medical research ethics committees, and may require us to revise and standardize ethical guidelines worldwide for the conduct of such research. The weighing of harm versus benefit of research as traditionally considered on an individual level needs to be considered on a population level for infectious diseases DURC, and on a global level due to the potential for transmissible infections to cause a pandemic, thus affecting people in places far from where the research was conducted. The harm of such research could result from either laboratory accidents or bioterrorism. As an example, engineered organisms such as influenza could result in an unnatural pandemic, affecting and harming people who were never informed of the research nor consented to it. The debate to date has been held among medical researchers and has been focused on the rights of researchers and scientific freedom. The community is also a stakeholder with rights, and DURC done in one country could cause harm to people in other countries who were never included in the debate. The first requirement is to inform and engage the public as a stakeholder in such research, and to make deliberations about DURC public and transparent. Secondly, governance structures and guidelines are not uniform internationally, and only some institutions and countries have specific DURC policies, none of which are enforceable. Consistent international guidelines and uniform, enforceable global governance models need to be developed for medical research ethics committees around potential population harm and benefit of DURC. Finally, researchers should be required to quantify potential population risks and benefits of DURC before it is approved. Models for quantifying risk–benefit equations could be drawn from health economics, with the onus on researchers to demonstrate that potential benefit outweighs potential harm. These would be positive steps towards protecting the interests and rights of all potentially affected populations in the case of transmissible infectious disease DURC. Past quantum changes in medical research governance such as mandatory registration of clinical trials show that major changes in research culture can be achieved. Current systems leave community stakeholders vulnerable to potential harms of infectious diseases DURC, and need to be addressed in a consistent and comprehensive manner internationally to ensure ethical obligations are met.

Keywords Dual-use research of concern · DURC · Genetic engineering · Infectious diseases · Influenza · Ethics

In the field of infectious diseases, acceleration in science has outpaced our legal and ethical frameworks. Dual-use research of concern is a term applied to life sciences research which is conducted with the intent of benefitting human health, but could also be misused to cause harm (Selgelid 2009; WHO). DURC is now a publicly available reality (Herfst et al. 2012; Imai et al. 2012). This includes creation of synthetic viruses, and since the 2011

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controversy over H5N1 avian influenza DURC, genetic engineering of pathogens that are not infectious to humans, to make them unnaturally infectious (Herfst et al. 2012; Imai et al. 2012). This new era in DURC raises questions about potential population-level harm to human beings which have not traditionally been considered by human research ethics committees or institutional review boards (IRBs), and may require us to revise systems and processes for conduct of such research. Whilst some individual scientific bodies, journals and institutions have created policies around DURC, there is no standardized approach to consideration of DURC when such research is proposed, nor to considering the population health impacts on a global level. In the USA, the 2004 Fink Report (National Research Council 2004) recommended the creation of a National Science Advisory Board for Biodefense. The NSABB was created and faced its first major challenge in 2011, over the controversy about publication of methods for engineered transmissible H5N1 influenza virus (Keim 2012). The concern is that if the methods for engineering potentially pandemic strains of influenza were made public, terrorists may use these methods to cause harm to populations. The NSABB initially recommended censorship of publication of full research methods, but later, after an outcry from scientists, reversed the decision in 2012 (Fedson and Opal 2013). The governance of DURC has been questioned after this decision, with questions raised about process, conflicts of interest, lack of transparency, and decision-making in the NSABB (Brown 2012; Roos 2014). DURC could potentially be self-regulated by scientists, or by government, or by a combination (Resnik 2010). It has been argued that self-regulation is flawed because of obvious vested interests and conflicts of interest which would heavily favour publication of DURC (Selgelid 2007; van Aken 2006). A combination of government and scientist regulation is preferable given the vested interests of medical researchers in regulating their own activities. Even a body such as the NSABB has limitations in its remit. In fact, the USA is the only country to have an advisory body such as the NSABB, which is advisory only, cannot enforce recommendations and has broad and sometimes ambiguous definitions of DURC (Dubov 2014; Resnik 2010). The NSABB has further been plagued with controversy after sacking members who were thought to be more likely to oppose DURC, has been accused of conflicts of interests, and has suffered significant reduction in scope and remit in 2014 (Roos 2014).

The example of influenza DURC is a good case study to illustrate the need for new approaches to considering and regulating DURC. Infectious diseases are unique because many are transmissible from human to human, and can cause epidemics and even pandemics within a relatively short period of time. Therefore, DURC involving contagious pathogens such as influenza can potentially impact people, populations, and countries far from the site of the research, who were not informed nor involved in the decision-making process. In 2013, a group of vaccine researchers petitioned the US president's bioethics committee, arguing that influenza DURC and other such research were "morally and ethically wrong" (Roos 2013). There are several ethical dimensions to such research. Influenza DURC and publication of such methods is associated with an unknown probability of resulting in an unnatural human pandemic (Osterholm and Henderson 2012), which would result in people who were never consulted and never consented to the research being affected. An unnatural pandemic could occur as a result of a either a laboratory accident or deliberate release by terrorists who reproduce published DURC methods. During the 2011 H5N1 controversy, scientists in favour of DURC publication argued that such research was safe and that laboratories could be trusted to avoid accidents. Yet in 2014 alone, four serious safety breaches involving anthrax, smallpox, avian influenza, and most recently Ebola, in leading laboratories in the US CDC and the NIH, show that the risk of laboratory accidents is real (Reardon 2014; Sun and Achenbach 2014). Bioterrorism with infectious diseases has occurred throughout human history and remains an ongoing threat (Alibek and Handelman 1999; Török et al. 1997). However, the current acceleration of DURC and public availability of methods for engineering of viruses raises the risk to new levels, by increasing the accessibility of such methods by those who wish to use it for nefarious purposes (Osterholm and Henderson 2012). It is timely to review the additional population health ethical considerations raised by infectious diseases DURC, and processes for approval of such research.

Modern medical research ethics committees originate from the Nuremberg code and the 1964 declaration of Helsinki, incorporating the lessons learned from Nazi Medicine (Hanauske-Abel 1996). The development of medical research ethics has been influenced mainly, and rightly, with a focus on the individual patient and interventions which only affect patients subjected to that intervention. The fundamental principles of voluntary informed consent of the human subject in medical research, assessing risk against expected benefit, avoidance of unnecessary pain and suffering and avoidance of actions that injure human patients are accepted in medical ethics, but have not been well considered on a population level as they pertain to infectious diseases and contagion (World Medical Association 2013). Influenza DURC involves animal research and would generally be submitted to animal ethics committees for initial consideration. These committees focus on the ethics of animal research and

avoidance of unnecessary harm and suffering to animals. If the overarching institutions of animal ethics committees, or the funding body, have a DURC policy, the application would then be referred for specific consideration of the risks versus benefits to human populations. However, referral to a HREC for consideration of population-level harm to humans as an ethical issue is not routine. HRECs could mandatorily be tasked with considering the potential benefits (such as development of drugs and vaccines) and the potential harms of DURC at the population level. They could use a harm–benefit framework to consider ethical aspects of animal infectious diseases DURC for human beings.

Research which generates newly transmissible pathogenic organisms raises ethical issues that go well beyond the individual patient. It is true that individual treatments, for example, anti-hypertensive medications, can have an impact on populations when they are recommended in policy or guidelines—however, even in this case, each individual who commences these medications makes an individual, informed choice after consultation with their physician to do so, and their decision does not impact on other people. This is not the case with a dangerous transmissible pathogen capable of causing a pandemic, where the initial research is in animals, but where human beings who were never informed and who never made any choice around the matter may become infected. Further, decisions made by a research regulatory body in one country may have ramifications around the world in the case of a pandemic.

It has been argued that to date, deliberations around DURC have been cloaked in secrecy and lacked transparency (Dubov 2014). It is important to acknowledge that it is not only the health sector and scientists who are stakeholders in infectious diseases DURC. DURC raises an ethical concern for which all of humanity are stakeholders, and yet are kept outside of the debate, which has publicly raged almost exclusively between health and medical research stakeholders (Fouchier et al. 2012; Osterholm and Henderson 2012). The public have a high level of trust in medical research and in the health systems which serve them, and as a scientific community, we have an ethical obligation to ensure that they are adequately informed and have a voice as stakeholders. Given that all people in the world are stakeholders in the potential benefits and harms of the creation of transmissible pathogens with pandemic potential, one could argue that there needs to be informed consent from the population about research which may inadvertently affect them. At the least, the public interest and rights of populations should be considered in such research.

Whilst it is difficult to gain informed consent from a whole population for DURC, this does not remove the ethical obligation to do so. One approach is to task community representatives on HRECs with advocating for the community interest, but this may not be adequate. Beyond this, other approaches may include public consultation, where submissions are called upon and some parts of the deliberations of HRECs are made public for DURC, in the same way that the deliberations of Institute of Medicine panels or the Advisory Committee on Immunization Practices (ACIP) are made public (CDC 2014). In these examples, the public consultation and transparency are driven by the recognition of the significant interests of the public as stakeholders. Public registration of DURC along the same lines as mandatory clinical trial registration could also be considered. These would be positive steps towards transparency and informing and engaging the community as a stakeholder in DURC.

Another supplementary approach to considering such research includes requiring researchers to quantify potential population risks and benefits, using available data and probability theory, and make these equations public before dual-use research is approved. Models for quantifying risk–benefit equations could be drawn from health economics and the requirements for government subsidization of medications in many countries (Beutels et al. 2008). Risk analysis is rarely used in medicine and health as it is in other disciplines, but models to quantify the probabilities of benefits and harms for DURC could be quite feasibly developed using risk analysis methods (Lipsitch and Inglesby 2014).

Finally, inconsistencies in governance and regulation of DURC around the world and between institutions must be addressed for the global risks of DURC to be meaningfully tackled. Specific internationally uniform and enforceable guidelines and global governance systems need to be urgently developed for IRBs and HREC's around potential population harm and benefit of DURC to ensure that the interests and rights of all potentially affected populations are considered in the spirit of the Declaration of Helsinki. DURC, which has an associated risk of harm to populations through contagion, is a new challenge for medical research ethics and requires us to abide by the accepted principles of consent, beneficence, and avoidance of harm. Achieving a new model for ethical governance of DURC is achievable when the example of clinical trial registration is considered historically. A decade ago, public registration of clinical trials was the exception, not the norm. Today, with a concerted global effort, funding agencies, medical journals, and institutions all work together in unison to ensure that an unregistered trial would be very unlikely to get funded or published in a reputable journal. Looking further back historically, the requirement for informed consent of human subjects in medical research and onus of proof on researchers to show avoidance of harm were not present

prior to the Nuremberg doctors trials and the development of the Nuremberg code, the precursor to the Declaration of Helsinki. These are now internationally consistent requirements that are enforced by human research ethics committees everywhere and accepted by the scientific community. Therefore, it is possible to create a new global accountability and governance for DURC in response to rapid recent acceleration in the science of such research. In summary, the key elements of such an approach include mechanisms for informing and consulting with the public as a stakeholder; requirements for researchers to quantify the risks and benefits of DURC; and standardization of enforceable international guidelines and governance structures for DURC globally in recognition of the potential global impact of engineered transmissible pathogens. The potentially serious risk to the global community posed by DURC cannot be minimized or trivialized for the personal benefit of scientists involved in DURC. There is an ethical obligation to address the governance of DURC globally and collaboratively, in a transparent manner which is free of conflicts of interest.

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References

Alibek K, Handelman S (1999) Biohazard: the chilling true story of the largest covert biological weapons program in the world—told from inside by the man who ran it (Reprint ed.). Delta book, Dell Publishing, Random House, New York

Beutels P, Scuffham P, MacIntyre C (2008) Funding of drugs: do vaccines warrant a different approach? Lancet Infect Dis 8(11): 727–733

Brown T (2012) H5N1 Flu expert takes issue with NSABB approach. Medscape Medical News. http://www.medscape.com/viewarticle/762183. Accessed Dec 2014

CDC (2014) ACIP Meeting Information; Advisory Committee on Immunization Practices (ACIP). http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html

Dubov A (2014) The concept of governance in dual-use research. Med Health Care Philos 17(3):447–457

Fedson DS, Opal SM (2013) The controversy over H5N1 transmissibility research. Hum Vaccin Immunother 9(5):977–986

Fouchier RAM, Garcia-Sastre A, Kawaoka Y (2012) Pause on avian flu transmission studies. Nature 481(7382):443

Hanauske-Abel HM (1996) Not a slippery slope or sudden subversion: German medicine and national socialism in 1933. BMJ 313(7070):1453–1463

Herfst S, Schrauwen EJA, Linster M, Chutinimitkul S, de Wit E, Munster VJ et al (2012) Airborne transmission of influenza A/H5N1 virus between ferrets. Science 336(6088):1534–1541

Imai M, Watanabe T, Hatta M, Das SC, Ozawa M, Shinya K et al (2012) Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature 486(7403):420–428

Keim PS (2012) The NSABB recommendations: rationale, impact, and implications. mBio 3(1):e00021–12

Lipsitch M, Inglesby TV (2014) Moratorium on research intended to create novel potential pandemic pathogens. mBio 5(6): e02366–14

National Research Council (2004) Biotechnology research in an age of terrorism. The National Academies Press, Washington. http://books.nap.edu/catalog/10827/biotechnology-research-in-an-age-of-terrorism

Osterholm MT, Henderson DA (2012) Life sciences at a crossroads: respiratory transmissible H5N1. Science 335(6070):801–802

Reardon S (2014) Safety lapses in US government labs spark debate. Nature. http://www.nature.com/news/safety-lapses-in-us-government-labs-spark-debate-1.15570

Resnik D (2010) Can scientists regulate the publication of dual use research? Stud Ethics Law Technol 4(1):Article 6

Roos R (2013) Scientists seek ethics review of H5N1 gain-of-function research. CIDRAP News. http://www.cidrap.umn.edu/news-perspective/2013/2003/scientists-seek-ethics-review-h2015n2011-gain-function-research

Roos R (2014) Wholesale roster change coming for US biosecurity board. CIDRAP News. http://www.cidrap.umn.edu/news-perspective/2014/2007/wholesale-roster-change-coming-us-biosecurity-board

Selgelid MJ (2007) A tale of two studies: ethics, bioterrorism and the censorship of science. Hastings Cent Rep 37(3):35–43

Selgelid MJ (2009) Dual-use research codes of conduct: lessons from the life sciences. NanoEthics 3(3):175–183

Sun LH, Achenbach J (2014) CDC reports potential Ebola exposure in Atlanta lab. The Washington Post. http://www.washingtonpost.com/national/health-science/cdc-reports-potential-ebola-exposure-in-atlanta-lab/2014/12/24/f1a9f26c-8b8e-11e4-8ff4-fb93129c9c8b_story.html?postshare=7491419455093730

Török TJ, Tauxe RV, Wise RP et al (1997) A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. JAMA 278(5):389–395

van Aken J (2006) When risk outweighs benefit: dual-use research needs a scientifically sound risk–benefit analysis and legally binding biosecurity measures. EMBO Rep 7:S10–S13

WHO (2014) Dual use research of concern (DURC), World Health Organization. Retrieved 12 Dec 2014, from http://www.who.int/csr/durc/en/

World Medical Association (2013) Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310(20):2191–2194